What's new in TB?

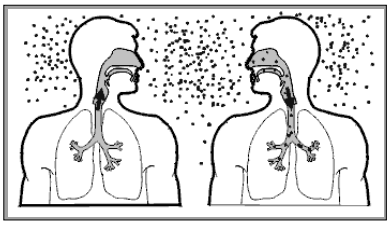
Max Salfinger
Wadsworth Center
New York State Department of Health
NLTN - December 14, 2005

Axelrod Institute, Wadsworth Center, NYS Department of Health

'Tuberculosis is a social disease with a medical aspect.'

Sir William Osler
1849-1919

Transmission



Sick
↑
Infected
↑
Healthy Persons

Natural History of TB

- 10% of infected persons with normal immune systems develop TB at some point in life
- HIV strongest risk factor for development of TB if infected
  - Risk of developing TB disease 7% to 10% each year
- Untreated TB, 50% will die

Tuberculosis – WHO data

- One third of world's pop. infected
- 8 Million new cases each year
- 2 Million deaths each year

Cost of Caring for TB Patients in US

- Drug susceptible case:

  $ 22,000 [N=32, 1992 $]

- Multidrug-resistant case (salvage therapy):

  $ 180,000 [N=35, 1990 $]

Am J Infect Control 23:1-4(1995); JAMA 270:65-68(1995)

PHL Fast Track Programs since 90s

- State-of-the-art laboratory procedures
- Shortest turnaround time
- All patients with newly diagnosed AFB smear-positive sputum are eligible

sees a doctor

1 Tuberculosis? Chest x-ray History / physical exam

2 RIF resistance?

3 Time to negativity? Adherence/Cure

Follow up specimens

Follow up specimens I

- Follow up specimens until 2 consecutive specimens are culture negative:
- AFB smear negative: at least once a mo
- AFB smear positive: bi-weekly

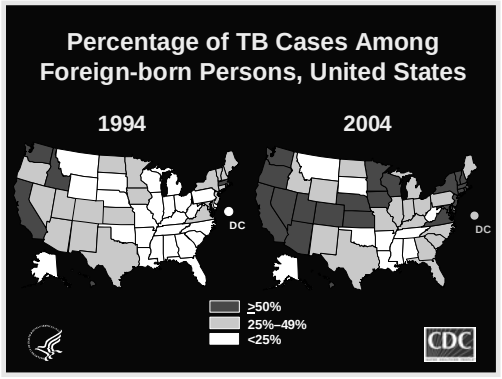
2 sputum specimens per event (NYS)

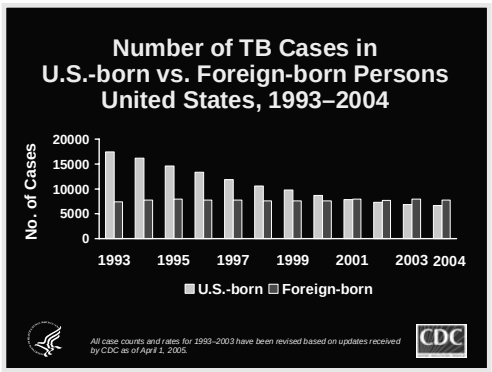
Follow up specimens II

- Follow up specimens until 2 consecutive specimens are culture negative...
- Initial cavitation & mo-2 culture pos: extend INH/Rif from 4 to 7 months
- Repeat susceptibility testing after 3 mo
- Pos culture @ mo-4: Treatment failure

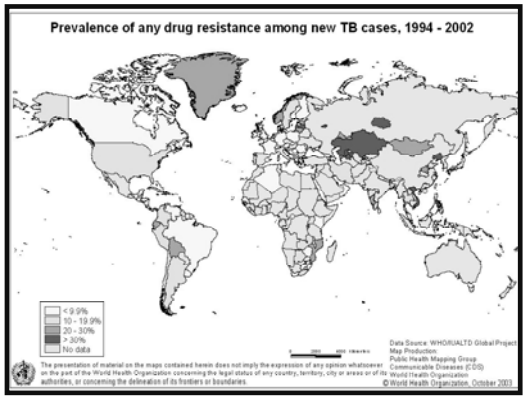
'Global village'

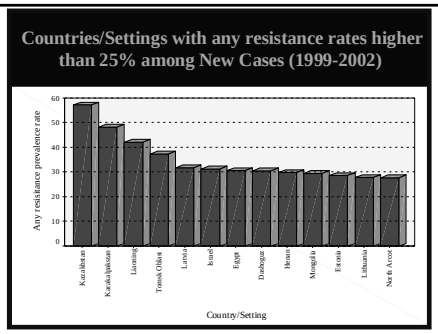
Marshall McLuhan, 1911-1980





DR TB





Hot Spots: Eastern Europe, Central & Southeast Asia

Treatment of MDR TB:

- **A regimen of <u>3-4 drugs</u> to which the isolate is <u>susceptible</u>**
- **<u>18 to 24</u> months <u>beyond</u> culture conversion**

Am. J. Respir. Crit. Care Med.; <u>167</u>:603-662(2003)

Florida MDR TB (1994 - 1997):

Chart Review [N=81]:	**<u>Cured</u>**
Community Care [N=31]	**48%**
A.G. Holley Hospital [N=39]	**79%**

Narita et al CHEST <u>120</u>:343-348(2001)

RIF resistance

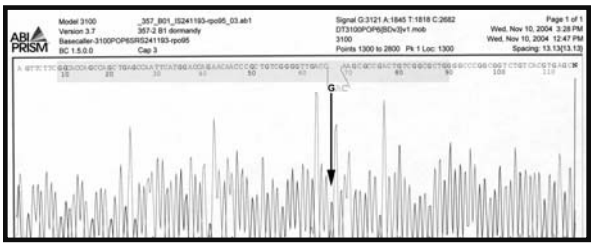
yes

or

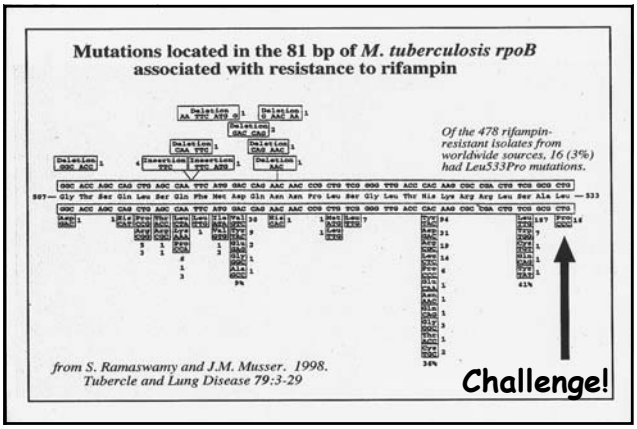
no ?

- **Clinical course**
- **Egg based AST**
- **Agar based AST**
- **Radiometric / Non-r.**
- ***rpoB* analysis**

rpoB analysis



Codon 526 (CAC) encodes histidine in sus. strain replaced with (GAC) aspartate in res. strain.



Molecular testing:

Drug	Gene	% mutations
RIF	*rpoB*	>96%
PZA	*pncA*	97%
INH	*katG*	40-60%
INH-ETH	*inhA*	15-43%
INH	*ahpC*	10%
INH	*kasA*	unknown

Drug-Resistant TB -

A Survival Guide For Clinicians

Francis J. Curry National Tuberculosis Center, San Francisco, 263 p. (2005)

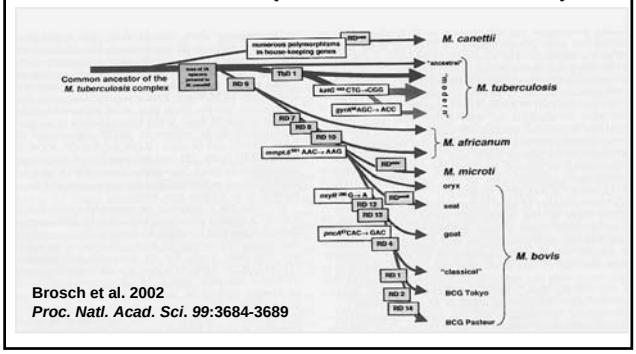
www.nationaltbcenter.edu

TBC

NAA, AccuProbe, and 16S sequencing detect <u>all</u> members of *M. tuberculosis* complex

- *M. tuberculosis*
- *M. bovis*
- *M. bovis* BCG
- *M. africanum*
- *M. caprae*
- *M. microti*
- *M. canettii*
- *M. pinnipedii*

Proposed Evolutionary Pathway of the Tubercle Bacilli (successive loss of DNA)



Brosch et al. 2002
Proc. Natl. Acad. Sci. 99:3684-3689

PCR based genomic deletion analysis for TBC members

Selected RD regions for Differentiation of the TBC

	RD1	RD9	RD10	RD4	RD5	RD12
MTB	+	+	+			
AFR	+	-	+ / -	+	+ / -	+
CAP	+	-	-	+	-	-
BOV	+	-	-	-	-	-
BCG	-	-	-			

Parsons et al. 2002
J. Clin. Microbiol. 40:2339-2345

Screening 1,685 Clinical Isolates belonging to the TBC (2001-2004)

	No.	(Percent)
▪ ***M. tuberculosis***	1,594	(94.6%)
▪ ***M. africanum***	31	(1,8%)
▪ ***M. bovis***	36	(2.1%)
▪ ***M. caprae***	1	(0.1%)
▪ ***M. bovis* BCG**	23	(1.4%)

Human tuberculosis caused by *Mycobacterium bovis* - New York City 2001 - 2004

Winters et al. 2005 *MMWR* 54:605-608

NAA

Nucleic acid amplification

- FDA approved:

  Smear-pos (Dec 1995)
  Smear-neg* (Sep 1999)

- MMWR July 7, 2000 [R]
- AFB-pos / NAA-neg
- AFB-neg* / NAA-pos

HEALTHY PEOPLE 2010

14-14 Reduce TAT for laboratory Dx

Target: 2 d for 75%

[21 d // '96]

U.S. Department of Health and Human Services, January 2000

Errors

Review of false-positive cultures for Mtb and recommendations for avoiding unnecessary treatment

Burman & Reves, Clin Infect Dis 2000, 31:1390-1395

Results:

- 14 studies with 100+ patients (12 incl. DNA typing)
- Definitions for false-positive vary
- Median false-positivity rate: **3.1%** (interquartile range 2.2% to 10.5%)

Pioneer from Harvard

'Errors must be accepted as evidence of systems flaws not character flaws. Until and unless that happens, it is unlikely that any substantial progress will be made in reducing medical errors.'

Leape, JAMA 1994, 272:1851-1857

TB fingerprinting

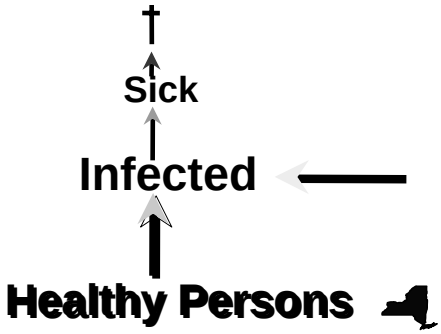
Universal, real-time Genotyping

National TB Genotyping and Surveillance Network

- Spoligotyping / MIRU
- Conventional RFLP

What have been the most useful aspects of universal DNA fingerprinting of M.tb?

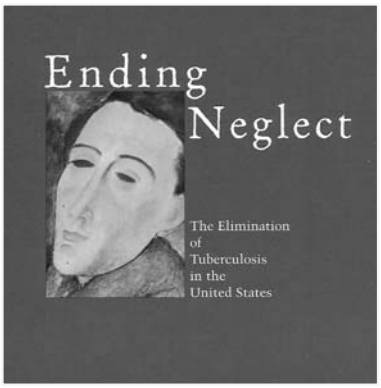
- Detecting false positive cultures
- Uncovering previously unrecognized cases of transmission
- Assessing efficacy of TB Control programs



Tuberculin PPD-S

Dr. Florence B. Seibert, 1897-1991
Henry Phipps Institute
1959 retired, St.Petersburg

1940 Produced PPD-S (Standard)
1941 US Standard
1952 WHO Standard



Institute of Medicine 2000

From TB control to TB elimination!

Elimination:

< 1 case

per 1 million pop

per 1 year

'… the greatest needs in the US are new diagnostic tools for the more accurate identification of individuals who are truly infected and who are also at risk of developing TB.' IOM Report 2000

Interferon Gamma assays

Pai et al. Lancet ID 4:761-776(2004)

- QuantiFERON-TB

FDA approval: November 2001

CDC guidelines: MMWR Vol 52 (RR-2) Jan 31, 2003 [R]

- T-SPOT.TB

Not FDA approved

Performing the assay:

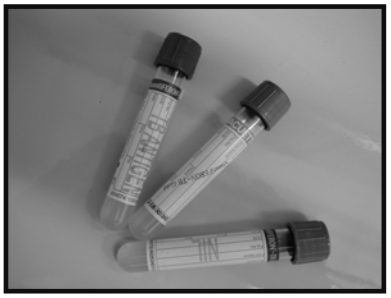
- I Blood collection (heparin)
- II Incubation of blood with stimulating antigens (ESAT-6, CFP-10)
- III Interferon gamma ELISA
- IV Interpretation

QuantiFERON Test:

Pros: 1) requires only one visit, 2) simple format, 3) more objective than TST

Cons: 1) antigens not TB-specific (M. kansasii; M. szulgai, M. marinum, 2) set up <12 hrs, 3) clinical experience limited

Interferon Gamma Assay



Processing sputum

Left over sediment used for molecular work-up - can you believe it?

Postmarketing surveillance

No systematic postmarketing surveillance for FDA approved assays - can you believe it?

TB meningitis

The sensitivity of laboratory assays is inversely proportional to the seriousness of the disease? - No improvement around the corner!

'It is health

which is real wealth

not pieces of silver and gold'

Mahatma Gandhi, 1869-1948

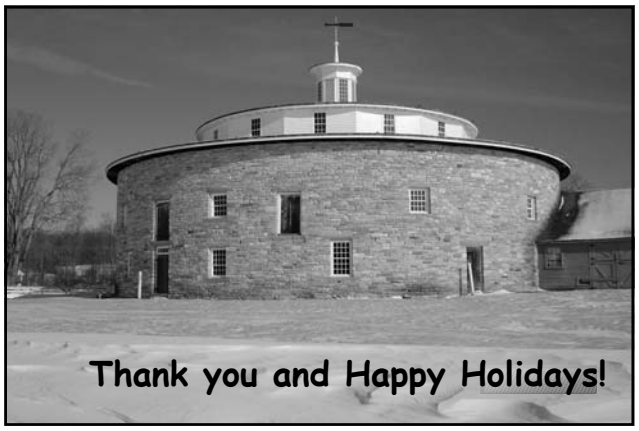
Working together

PHL Fast Track Programs,2005:

- **State-of-the-art laboratory procedures**
- **Shortest turnaround time**
- **All patients with newly diagnosed AFB smear-positive* sputum**
- **All patients with suspected drug-resistant TB**

- **Fighting TB**
- **Fighting poverty**
- **Standing up for**

PEACE On Earth!


Thank you and Happy Holidays!